9

Summary and future perspectives

Chapter 9

Summary

In this chapter, data from this thesis are summarized. In addition, perspectives and strategies for future research are discussed. The subject of the first part is long-term and late cardiovascular toxicity in testicular cancer survivors. In the second part the focus lies on the development and organization of survivorship care.

Part I

Long-term side-effects of platinum-based chemotherapy

Testicular cancer represents a malignancy with high cure rates, even in advanced stages. Since the introduction of platinum-based combination chemotherapy in the late 1970s, the survival rate of patients with disseminated disease has increased considerably and is currently above 80%. Because testicular cancer is usually diagnosed around the age of 30 years, these men can expect to live for another 40 to 50 years after being successfully treated. However, the success of cisplatin-based chemotherapy comes at the price of long-term and late effects related to healthy tissue damage. In **chapter 2**, we reviewed the current knowledge on late effects of platinum-based treatment for patients with testicular cancer. Secondary malignant neoplasms and cardiovascular disease represent the most common potentially life-threatening late effects, sometimes occurring ten or more years after treatment. Cardiovascular impairment and cardiovascular disease are often preceded by the gradual development and presence of cardiovascular risk factors, clustered into the metabolic syndrome. Other long-term effects are pulmonary toxicity, nephrotoxicity, neurotoxicity, decreased fertility, hypogonadism and psychosocial problems. The incidence and time of onset of these various late adverse effects vary according to treatment type and intensity. In this review, the current knowledge was described regarding different somatic and psychosocial long-term late effects after treatment for testicular cancer. Recommendations were given for medical evaluations that begin after treatment is completed and continue during follow-up.

Circulating platinum remains detectable in serum up to twenty years after the administration of platinum-based chemotherapy.[1] Direct toxic effects may in part explain the increased incidence of cardiovascular disease in testicular cancer survivors, as well as the development of second tumors.[2-4] In **chapter 3**, serum platinum decay after chemotherapy was assessed and modelled and relationships between long-term circulating platinum levels and known late effects were determined. In 99 testicular cancer survivors, treated with cisplatin-based chemotherapy, serum and 24-h urine samples were collected during follow-up ($_{1–13\ years}$ after treatment). To build a population pharmacokinetic model, measured platinum data were simultaneously analyzed, together with cisplatin dose, age, weight and height using the NONMEM software. Based on this model, the Area Under the Curve for platinum between 1 and 3 years after treatment (Pt $AUC_{1–3\ years}$) was calculated for each individual patient. Predicted long-term platinum exposure was compared with renal function and late effects of treatment assessed median 9 (3–15) years after chemotherapy. Decay of platinum was best described by a two-compartment

model. Mean terminal $T_{1/2}$ was 3.7 years (range 2.5–5.2). Pt $AUC_{1\text{-}3\ years}$ correlated with cumulative cisplatin dose and creatinine clearance before and 1 year after treatment. Patients with paresthesia had higher Pt $AUC_{1\text{-}3\ years}$ (30.9 versus 27.0 µg/l month) compared with those without paresthesia (P = 0.021). Patients with hypogonadism, elevated LDL-cholesterol levels or hypertension also had a higher Pt $AUC_{1\text{-}3\ years}$. It was concluded that renal function before and after cisplatin treatment appeared to be an important determinant of long-term platinum exposure. Known long-term effects of testicular cancer treatment, such as paresthesia, hypogonadism, hypercholesterolemia and hypertension, are associated with long-term circulating platinum exposure. No safe dose can be defined for platinum-based chemotherapy, as the association is continuous.

Identifying patients susceptible to cardiovascular toxicity

Chemotherapy-treated testicular cancer survivors are at risk for development of the metabolic syndrome, especially in the case of decreased androgen levels. Genetic susceptibility may influence the risk of metabolic syndrome in testicular cancer survivors. Polymorphisms in the gene encoding steroid 5-α-reductase type II (*SRD5A2*) are involved in altered androgen metabolism. In **chapter 4**, it was investigated whether single-nucleotide polymorphisms (SNPs) rs523349 (V89L) and rs9282858 (A49T) in *SRD5A2* are associated with cardiometabolic status in testicular cancer survivors. In 173 chemotherapy-treated testicular cancer survivors, hormone levels and cardiometabolic status were evaluated cross-sectionally (median 5 years (range 3–20) after chemotherapy) and correlated with SNPs in *SRD5A2*. The metabolic syndrome was more prevalent in survivors who were homozygous or heterozygous variant for rs523349 compared to wild type (33% versus 19%, *P* = 0.032). In particular, patients with lower testosterone levels (<15 nmol/l)* (at time of analysis this was considered to be the level for (subclinical) hypogonadism and best discriminating for metabolic syndrome) in combination with a variant genotype showed a high prevalence of the metabolic syndrome (66.7%). Mean intima-media thickness of the carotid artery and urinary albumin excretion, both markers of vascular damage, were higher in the group of survivors homozygous or heterozygous variant for rs523349 (0.62 versus 0.57 mm, P = 0.026; 5.6 versus 3.1 mg/24h, P = 0.017, respectively). No association was found between cardiometabolic status and SNP rs9282858 in *SRD5A2*. It was concluded that metabolic syndrome develops more frequently in testicular cancer survivors homozygous or heterozygous variant for SNP rs523349 in *SRD5A2*. Altered androgen sensitivity appears to be involved in the development of adverse metabolic and vascular changes in testicular cancer survivors and is a potential target for intervention.

Cardiovascular disease threatens testicular cancer patients not only years after the treatment, but also during and shortly after chemotherapeutic treatment. To prevent cardiovascular disease, high-risk patients should be identified. The aim of the study in **chapter 5** was to assess vascular damage induced by bleomycin-etoposide-cisplatin (BEP)-chemotherapy and to find risk factors for early vascular events. A prospective cohort study was performed in (B)EP treated testicular cancer patients. Development of venous and arterial vascular events was assessed. Vascular damage markers (von Willebrand factor [vWF], coagulation factor VIII [FVIII], intima media thickness [IMT]) and cardiovascular risk factors were assessed before, during and until 1 year after

chemotherapy. Before start of chemotherapy a vascular fingerprint was estimated as a risk model to predict cardiovascular morbidity during chemotherapy. Presence of ≥ 3 out of 5 risk factors was defined as high-risk vascular fingerprint: body mass index > 25 kg/m^2, current smoking, blood pressure >140/90 mmHg, total cholesterol > 5.1 and/or low-density lipoprotein > 2.5 mmol/L or glucose ≥ 7 mmol/L. Seventy-three patients were included. Eight patients (11%) developed vascular events (four arterial events, four pulmonary embolisms). vWF and FVIII increased during chemotherapy, especially in patients with vascular events. Sixteen patients (22%) had a high-risk vascular fingerprint before start of chemotherapy. These patients had arterial events more often (3/16 [19%] versus 1/57 [2%]; $P = 0.031$) and higher vWF levels and IMT. Endothelial activation and upregulation of procoagulant activity seem important mechanisms involved in early BEP-chemotherapy-induced vascular events. Before chemotherapy, one quarter of the patients already had cardiovascular risk factors. A vascular fingerprint could identify patients at risk for arterial events. This vascular fingerprint, when validated, can be used as a tool to select high risk patients who may benefit from preventive strategies. Currently, a multi-center trial is ongoing to validate the vascular fingerprint risk score.

Part II

Survivorship care planning and organization

In 2006, the Institute of Medicine recommended the use of a survivorship care plan (SCP) to organize follow-up care after cancer treatment. An SCP offers patients and their healthcare providers an overview of the diagnosis, the received treatment and future follow-up care. Unfortunately, it has proven to be difficult to implement SCP's into practice. The outcome of several studies provided no clear evidence for the benefit of SCP's and there is no consensus about the content of the document. There is still an ongoing debate about how to evaluate the use of SCP's. In an editorial, Parry *et al*. argued that by focusing too much on SCP's as a document, we have lost sight on the process of care planning.[5] We tend to forget the primary goal of an SCP in the first place: guiding follow-up care to ensure that survivors receive appropriate care after cancer treatment. They proposed a conceptual framework to guide research on survivorship care planning. In **chapter 6**, we replied to this editorial in a letter to the editor, in which we illustrated the use of a mobile application that we developed. This mobile application serves as a carrier for a digital SCP. It enables patients to play a central role in their own survivorship care and brings patients, medical oncologists and primary care physicians together in the process of care planning.

In **chapter 7**, the development and use of this application, the Survivor Care app, is further explained. The aim in this study was to develop a simple and smart, mobile application to provide a personalized SCP to testicular cancer survivors, participating in a shared-care survivorship program. The content of the SCP is based on guidelines for testicular cancer follow-up and recommendations of experts in the field of testicular cancer survivorship care. Requirements and wishes were discussed with healthcare providers and testicular cancer patients before and

during development. The mobile application was developed for the iOS (iPhone/iPad) platform. By scanning a QR code the mobile application can import an individual SCP generated by the oncology provider. Patients receive an interactive overview of their personalized follow-up plan. The care providers receive a copy. The SCP is generated based on data extracted from the electronic health record and using algorithms of survivorship guidelines. Both the web-based SCP generator and the mobile application can be used by other cancer centers worldwide and can be adapted for use in other tumor types. The care plan generator is available for other hospitals in the Netherlands and in other countries. Hereby, we launched and made available a mobile application and an accompanying web-based SCP generator (**survivorcare.umcg.nl**), which can be easily used to offer survivors and their healthcare providers a clear and personalized overview of survivorship care. With this digital SCP, survivors are getting more in control and it allows optimal coordination, planning, and navigation of required survivorship care.

Shared-care follow-up after testicular cancer

Testicular cancer survivors are prone for early development of cardiovascular risk factors during the years after the chemotherapeutic treatment. Therefore, close collaboration between oncologists and primary care physicians is needed during follow-up to monitor and manage these cardiovascular risk factors. Currently, survivorship care for testicular cancer survivors is mainly provided in larger oncology centers. In **chapter 8**, a shared-care survivorship program was described, in which testicular cancer patients visit both their oncologist and their primary care physician. The objective of this study was to test the safety and feasibility of shared-care follow-up after treatment for metastatic testicular cancer. The study was designed as an observational cohort study with a stopping rule to check for the safety of follow-up. Safety boundaries were defined for failure of an adequate response to signals indicating cancer recurrence. Secondary outcomes were cardiovascular risk management, psychosocial status and patient preferences as measured with an evaluation questionnaire. The mobile application, described in **chapter 7**, was applied in this study to provide participating patients with an SCP. In total 162 patients (69% of eligible testicular cancer patients) were enrolled and 241 primary care visits took place. Almost all (99%, n = 150) of the primary care physicians we approached agreed to participate. No failures occurred in detection of relapsed testicular cancer. Four follow-up visits were considered as failures because of organizational issues, without activation of the stopping rule. Patients were satisfied with the knowledge level of primary care physicians. Primary care physicians were willing to further extend their role in follow-up care after cancer. It was concluded that shared-care follow-up is safe and feasible in this patient population. Patients benefit from the personalized care, partly close to their home. Within shared-care, primary care physicians can have an important role in cardiovascular risk management and psychosocial survivorship issues.

Chapter 9 and **chapter 10** summarize this thesis in English and Dutch, respectively.

Future perspectives

Long-term side-effects of platinum-based chemotherapy

In this thesis, we described an association between long-term platinum levels and known late effects of platinum-based chemotherapy, such as hypertension, neuropathy and high cholesterol. The question remains whether this association is direct or indirect, i.e. whether long-term circulating platinum indeed plays an etiological role in the development of late toxicity. Various aspects deserve further research.

Firstly, platinum concentrations in other tissues, such as adipose tissue, have not yet been determined in testicular cancer survivors. From autopsy studies it is known that platinum can be found in multiple tissues in the body.[6] An interesting option would be to evaluate platinum concentrations in adipose tissue after platinum-based chemotherapy. It is conceivable that the long-term presence of platinum residuals in fat tissue may have an adverse metabolic effect that ultimately leads to the development of the metabolic syndrome. Although the quantity of platinum is very low, the exposure during up to two decades may result in significant toxicity. Apart from being depots for simple energy storage, fat tissues have different endocrine functions that are controlled by adipocytokines, such as leptin, adiponectin, PAI-1, TNF-α and interleukin-6. Visceral fat, more than subcutaneous fat, is regarded to play a central role in the etiology of the metabolic syndrome. Inflammatory patterns in adipose tissue differ between visceral fat and subcutaneous fat.[7] These patterns may be influenced differently by platinum retention.

Secondly, the decay of long-term platinum levels and renal function needs to be further elucidated. We found a correlation between long-term platinum levels and renal function. It is probable that an impaired renal function leads to less excretion of platinum, resulting in a higher long-term circulating platinum level and subsequent higher AUC. However, the determinants of long-term platinum excretion need to be further clarified. Longitudinal assessments of both renal function and platinum levels, both shortly after chemotherapy as well as during follow-up, could improve the accuracy of the population-pharmacokinetic model of long-term decay.

Finally, the association between long-term platinum and direct toxicity deserves further investigation. It is established that platinum-based chemotherapy causes vascular toxicity in long-term survivors.[3,4] It should be clarified if this damage is mainly caused during and shortly after chemotherapy or whether long-term circulating platinum has a significant contribution to the eventual vascular damage. Long-term circulating platinum is also a potential risk factor for the development of secondary tumors, especially in excreting organs (kidney and higher/lower urinary tract).[2,8] In a recent Norwegian study, a significant association was found between platinum decay after treatment and the risk of second cancers, as well as other late effects such as paresthesia and tinnitus.[9] These findings warrant further research on the relationship between long-term platinum and secondary tumors.

Genetic susceptibility to late toxicity

Ideally, each cancer survivor should receive survivorship care that is adjusted to his or her diagnosis and treatment plan and personal risk profile, based on the increasing amount of knowledge about long-term and late effects. Genetic susceptibility should be incorporated into this personal risk profile, but currently our understanding of genetic susceptibility to long-term and late toxicity is limited. In testicular cancer, most recent insights are reported concerning ototoxicity.[10] In chapter 4, we described an association between SNP rs523349 in *SRD5A2* and the prevalence of metabolic syndrome. This association was also found in a study population of patients with benign prostatic hyperplasia.[11] However, in two other studies in testicular cancer survivors, no association was found between hormonal status, respectively metabolic syndrome and SNP rs523349.[12,13] The follow-up duration at which the presence of the metabolic syndrome was assessed was different between our study and the study by Zaid *et al*. which makes it difficult to compare them. Nevertheless, it illustrates that such associations should be replicated and interpreted with caution. Validating the pharmacogenomics of chemotherapy-induced toxicity had proven to be difficult.[14] Instead of selective candidate gene studies, a hypothesis-free approach that is provided by genome-wide association studies (GWAS) limits the chance of false positive findings. But the GWAS approach is best suitable for large cohorts, whereas study cohorts of testicular cancer survivors are often small. International collaboration, such as the TECAC consortium, will hopefully provide future possibilities for large-scale genetic research in testicular cancer.[15] Data generated with these large-scale GWAS studies can subsequently be analyzed with the promising possibility of using system genetics as described by Atanasovska *et al*.[16] Another interesting option is the use of DEPICT, a computational integrative tool that systematically prioritizes the most likely causal genes at associated loci, based on predicted gene functions.[17] In the local OncoLifes project, germ-line DNA is prospectively collected in different patient populations before start of treatment. In the long-term, such initiatives will also provide opportunities for research regarding genetic susceptibility to long-term effects.

Survivorship care planning and organization

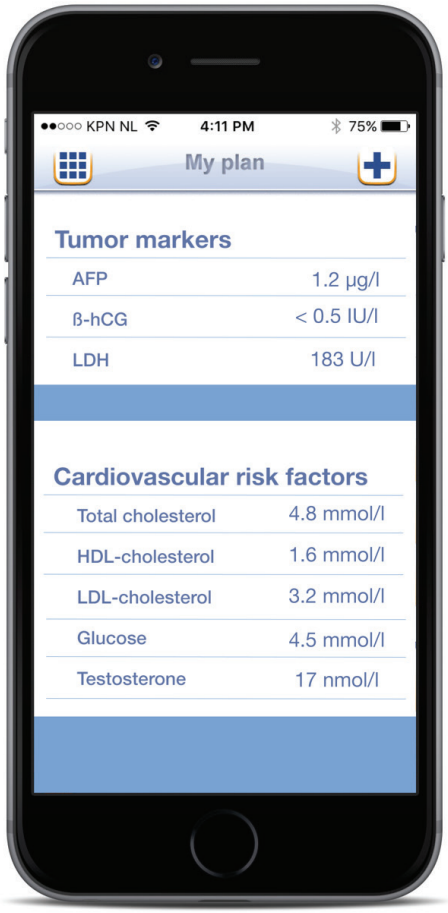
A survivorship care plan (SCP) provides patients and their healthcare providers an overview of the received treatment and a personal schedule for follow-up care. Several studies, including multiple randomized clinical trials (RCTs), evaluated the use of SCPs, but often these studies failed to a show a clear benefit.[18] This might be a consequence of the measured outcomes and that they were too much focused on the SCP as a document, instead of the intervention that can be supported by the use of an SCP. In some studies, the SCP contributed to improved communication with the primary care physician.[19] Also, the SCP can be regarded as a tool to organize care and as a behavioral intervention to encourage survivors to improve lifestyle and self-management.[20] In a recent systematic review of SCP studies, it was concluded that SCP studies targeted at new models of care, e.g. within primary care, are more likely to demonstrate a potential benefit of SCPs.[21] In line with this, in our shared-care program, the SCP was used as a navigating tool to support the hybrid follow-up of oncologist and primary care physician, combined with active involvement of the patient. The latter is the most valuable feature of the Survivor Care app. It enables patients to play

an active role in their own follow-up and it can be used as an instrument for behavioral change. Several suggestions will be discussed for further development of this navigating tool.

Firstly, in the current study laboratory assessments are performed in the oncology setting as well as in the primary care setting, without any direct feedback within the app. It would be a valuable improvement for the communication and organization of shared-care follow-up when patients would receive their laboratory results directly in the app, including both tumor markers and cardiovascular risk parameters (Figure 1). This electronic insight in the lab test results will also become available for patients in next-generation electronic patient health record systems (e.g. MyChart in EPIC), but integrating it as a function in the Survivor Care app makes it more intuitive for patients. A companying smart watch function can be used to inform patient with messages regarding laboratory results and appointments (Figure 2).

Recently, reports have been published in which the clinical benefit of patient-reported outcomes is demonstrated for monitoring of symptoms in routine oncology care.[22,23] A web-based tool that monitors self-reported symptoms improved overall survival in lung cancer patients due to early relapse detection and better performance status at relapse. Symptoms that can be monitored in the Survivor Care app are for example, back pain, paresthesia, mood and fatigue (Figure 2). This screening of symptoms can be used for individualizing care (although this results in a change in merits of the follow-up), but can also be used as a tool to collect patient reported outcome and follow-up data for research, for example in the Dutch PROFILES-registry (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship).[24 23] From this registry, data can easily be linked to data registered in the Netherlands Cancer Registry.

The digital SCP is generated on a worldwide availably website and imported into the patients' smartphone with a QR code. This simple and effective solution could tackle known barriers in the use of SCPs, such as lack of time and resources. A quick and compact "one-page" plan is better than large, complex plans.[25] This can motivate other cancer centers to actively use the SCP. Until now most centers do not yet use an SCP; a simple to use dummy-proof solution could be helpful to improve this situation. Also, patients could take the initiative to ask for an SCP and play a more prominent role in their own follow-up care.



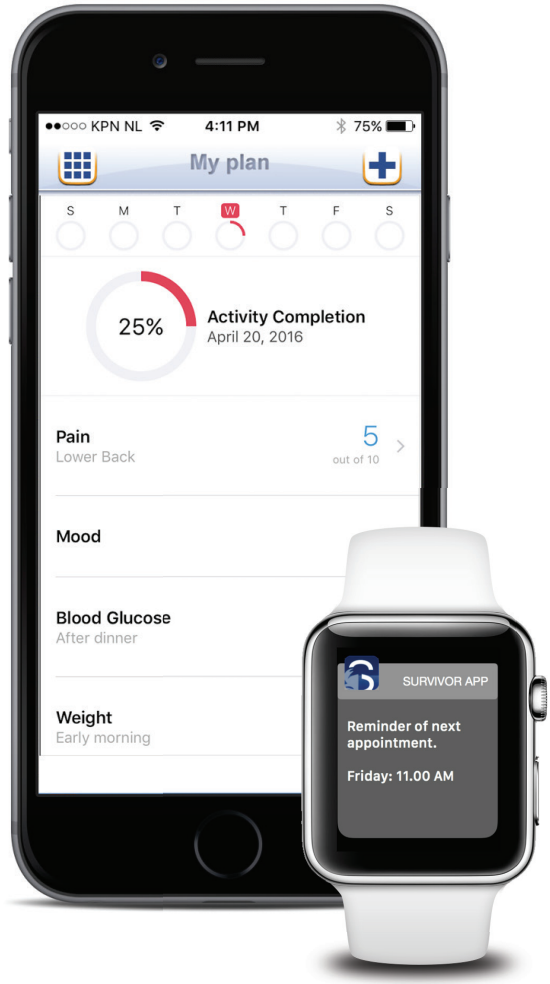


Figure 1 and figure 2

Shared-care follow-up after testicular cancer

Now the safety of shared-care follow-up is established for testicular cancer, the potential benefits of this type of follow-up could be further explored and the organization can be optimized based on acquired experiences. In general, the role of primary care in follow-up after cancer is expanding.[26] For testicular cancer, different directions for shared-care follow-up can be conceived. If the primary care physician is actively involved and motivated to collaborate in the follow-up, shared-care can be increased to intensify the collaboration between oncology and primary care. The number of visits in primary care could be extended to 50% of the total number of follow-up visits. Hereby follow-up care could be organized closer to home. In this model of care the financial reimbursement of primary care physicians should be ensured. The intention to extend the number of visits in primary care could be distilled from the evaluation among patients and primary care physicians of our shared-care trial. In future studies, cardiovascular risk management and psychosocial needs require further attention and research. The current shared-care follow-up program can be used as a comparator for future studies for testicular cancer survivors. A future study should be set-up as a randomized trial with a multiple-center organization to achieve the needed number of study participants and to broaden the implementation of shared-care follow-up.

Design concept: Patients that finish their treatment and are willing to participate in this type of shared-care follow-up are randomized in two groups: (1) survivorship care plan-based follow-up (with potential collaboration in shared-care with primary care physician) and (2) the current standard-care, oncologist-only follow-up. This concept idea is illustrated in Figure 3. The primary outcome will be cardiovascular risk status (as addressed by presence of metabolic syndrome as well as estimated lifetime cardiovascular risk three years after end of treatment). In the intervention group the oncologist will discuss the possibility of shared-care with the primary care physician. There are different options to organize the oncologic follow-up and the management of cardiovascular risk factors. Direct and clear communication between all parties, including the patient, is essential in the intervention group. Intervention advices will be clearly formulated in collaboration with vascular medicine when needed.

As pointed out in the systematic review by Jacobsen *et al*. many studies fail to demonstrate a benefit of SCP, partly as a consequence of choosing too distal outcomes measures.[21] More proximal outcome measures, such as adherence to the prescribed guideline, are more capable of showing differences that can be realistically expected. Secondary outcomes could be the effect of lifestyle interventions, persistence to lifestyle improvements, psychosocial questionnaires and adherence to follow-up guidelines. Lifestyle interventions play an important role in the prevention of adverse cardiometabolic changes.[27] A question that remains is to which extent lifestyle advices by primary care physicians and oncologists lead to improved cardiovascular risk profiles. The psychosocial aspects of follow-up also deserve further research. Patients could benefit from discussing psychosocial issues with their primary care physician or general practice-based nurse specialist. Subsequently, this might also lead to better referring to other supportive care providers such as social workers, physical therapists and lifestyle consultants.

With regard to organization a few suggestions for improvement arise from the performed shared-care trial. To improve the organization of a future study, the logistic organization could be simpler. Based on the performed shared-care program, a limited set of data is required after each

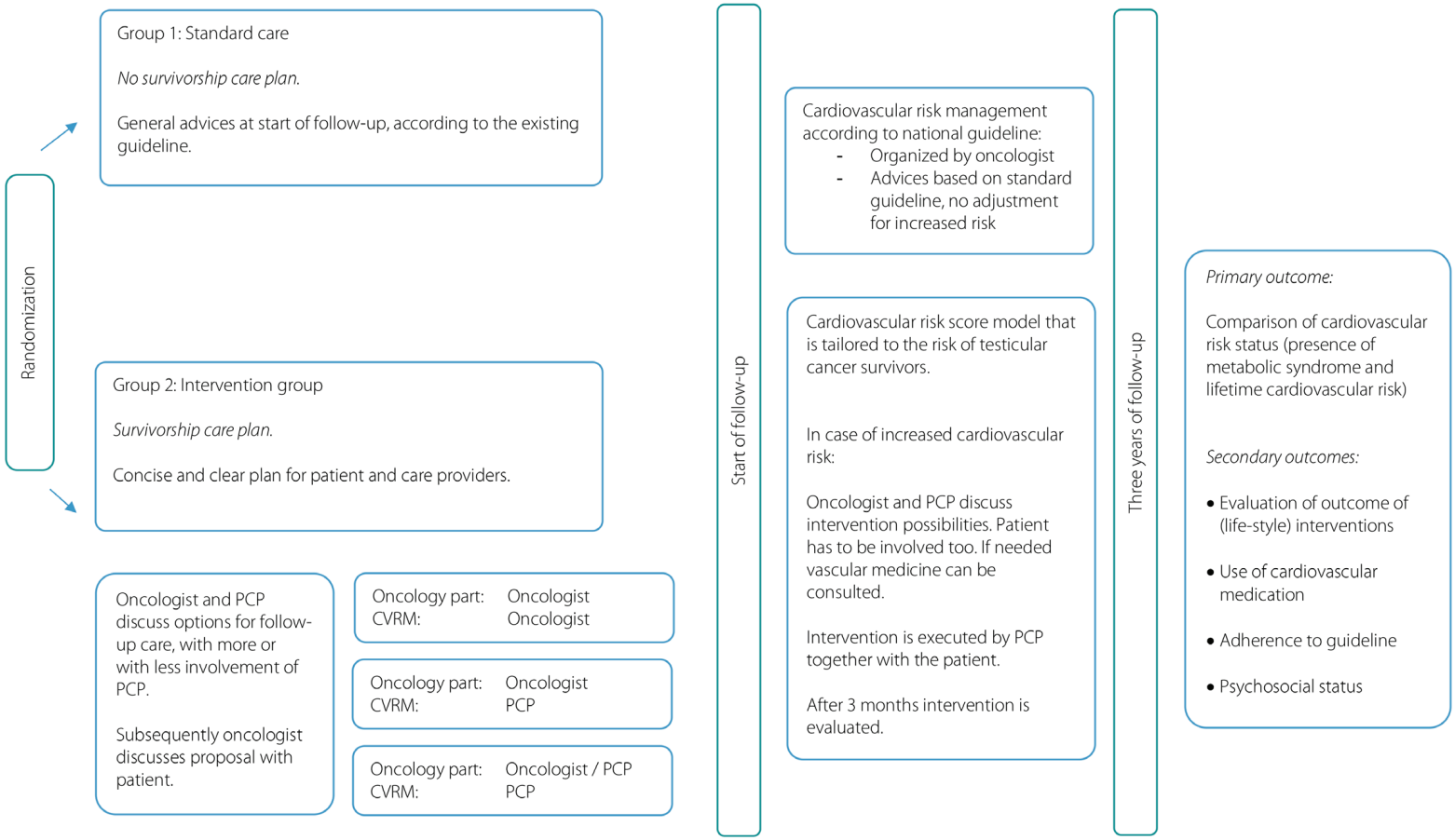
visit for safety monitoring. The essential required safety data are tumor markers values and the presence of specific symptoms indicating a possible relapse, such as unexplained lower back pain. The mobile application can be used to facilitate the data communication. Other data, such as cardiovascular risk data and psychosocial data can be collected with an interval.

In contrast to the performed shared-care program, shared-care follow-up could also be organized in a different, more simple way. Some issues that were observed were caused by primary care physicians doing work and logistics with which they were not familiar, in particular the aspects of oncologic follow-up care after testicular cancer. A better effect could be achieved if the patient would go to the primary care physician for cardiovascular risk management only, which is a more general issue in the daily practices of primary care physicians and with which they are more familiar. It is important to realize that primary care physicians have only one or two patients in their practice with a history of testicular cancer, but a significant proportion of patients with a history of cancer that are at risk for cardiovascular late effects. The follow-up care for testicular cancer patients could be organized in an 'add-on model' in which the roles of the different care providers are more separated. The benefit, among other things, is that this will probably decrease the risk of 'being lost in transition' after ten years in comparison with hospital-only follow-up. This add-on model is also useful for the group of patients that is less adequate in organizing their care themselves. When the system would be simpler, the primary care physician can play their role easier because he or she is more acquainted with his own territory. The disadvantage of this model will be that it leads to the need of double visits (for oncology purpose and for cardiovascular purpose, oncologist and primary care physician) and in the long-term the primary care physician will not be familiarized with the oncological aspects of follow-up.

To conclude:

Results from research described in this thesis increase the knowledge on long-term and late effects of treatment and contributes to the organization of survivorship care for testicular cancer patients. Gradually, we better understand the mechanisms behind the development of late toxicity. With these insights we can predict more accurately which patients are at risk for long-term and late effects of treatment. In time, these insights will personalize survivorship care, improve collaboration with the primary care physician and will give the patient more control of his own care.

Figure 3. *Concept for randomized clinical trial. Abbreviations: PCP, primary care provider.*



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